

Episode 014: Hormonal Contraceptives & Mental Health

David Puder, M.D., Dr. Mona Mojtahedzadeh



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There are no conflicts of interest for this episode.

Many women take hormonal contraceptives as a way of preventing pregnancy, or for other health reasons. These contraceptives basically use hormones to stop your body from ovulating.

But do you ever wonder if changing your hormones can affect more than just your chances of getting pregnant?

Birth control has many positive effects too, other than just preventing unwanted pregnancy. It can help with:

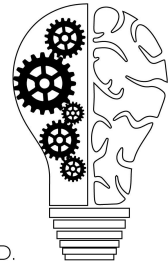
- Acne
- Depression in elderly
- Hirsutism
- Heavy periods
- Maintaining bone density
- Decreased risk of certain cancers
- Premenstrual dysphoric disorder

How hormones work without the pill

In a woman that's not on the pill, early in their cycle, they'll have the least amounts of estrogen and progesterone in their body. Around ovulation, estrogen will rise, which changes their mood, causing them to experience more of the reward hormone, dopamine, and even the happy hormone, serotonin. Later in the cycle, progesterone rises too, changing the emotional state again. The drop in hormones and Progesterone is the depressant hormone, so this is typically what causes the pre-period moodiness that some women feel.

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This hormonal shift does not happen, or happens very subtly in women who are on birth control.

Using a hormonal contraceptive changes your body's chemistry, and alters your hormones. When you change your body chemistry, you may have influences on your mood, desire, all sorts of things we wouldn't normally consider when we are only looking for the benefits.

Here are some of the things hormone contraceptives can effect:

What women find attractive

Scientists noticed that women who were ovulating, and not on the pill, had an increased attraction to more masculine faces, dominant male behavior, taller men, deeper voices, versus when they were not ovulating. Ovulating women also wanted to go to public events more, and had more sexual fantasies. When they weren't ovulating, women looked for a man who is more empathic, more fatherly, more compassionate.

Depression

One study followed a group of women for a number of years to see if their mood changed. They found that the younger (15-19) contraceptive group was 1.7-1.8 times more at risk of depression and being prescribed antidepressants. Specifically, younger women (15-19), and those who were prescribed progesterone-based pills, were at the highest risk of depression. Also, most of these women experienced the depression onset at around 2 months - 1 year.

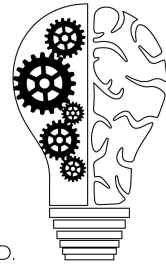
If you're older, taking a more estrogen-based hormone, have been on it for a while, and are not depressed and have been taking hormonal contraceptives for more than one year, I would say you are probably not at risk of developing depression because of contraceptives. Now, that said, there are tons of reasons that people get depressed—life situations, genetics, health—it's not just related to hormones. If you are concerned about depression, talk to your doctor about it.

Natural fear response

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Women who are on hormone contraceptives are more likely to experience anxiety. Natural hormone levels help with fear extinction, or the ability to overcome fears. Birth control can inhibit our ability to regulate fear in stressful situations.



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Empathy

In the part of the natural cycle, before ovulation, when estrogen is higher, women have an increased ability to recognize facial expressions of emotion. Hormonal contraceptives decrease brain responsiveness, making it more difficult to process emotion, and making recognition of negative emotions harder.

Reward Pathway

Ovulation also causes an increase in estrogen, which increases the brain reward pathways by increasing dopamine, our body's pleasure response hormone.

If you are on an oral contraceptive, the changes in hormones can cause a dampened reward processing, so there may be a decreased amount of pleasure you can experience through things like food, sex, or even social connectedness.

My conclusion about the pill

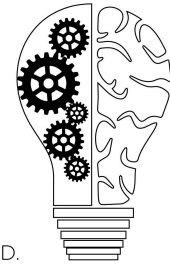
Overall, with the positive effects birth control has caused in society, namely, a decrease in teen pregnancy, it can be difficult how to integrate the new details emerging on the influence on mental health.

I know my research into this has led me to be more aware of teens I treat who are taking hormonal contraception. If you're looking for the benefits of the pill, there are many types of contraceptives, and because every woman is different, there is not a one-size-fits-all option. Talk to your doctor about which one is best for you.

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Below are more detailed notes that Dr. Mona Mojtahedzadeh and Dr. David Puder worked on together to provide the scientific foundation for this episode.



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Intro:

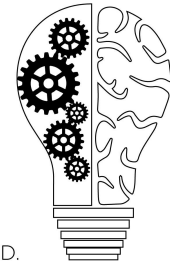
- Our goal is to empower women to know more about the recent debate in the relationship between contraception and mental health.
- I first started thinking about this after hearing a talk by Kelly Brogan
- Worldwide, 100 million women use “the pill”.
- Approximately 82% of sexually active women in the USA use oral contraceptive pills (OCP) sometime during their reproductive years.
- 17% of women aged 15-44 use “the pill”.
- The last decade in the USA, rates of teenage birth rate along with teenage pregnancy and abortion have decreased. Most researchers attribute this victory to improved access to contraception. (Carrol, 2017- New York Times)
- OCPs are prescribed for various reasons: prevention of unintended pregnancy; decreased risk of ovarian, endometrial, and colorectal cancers; preservation of bone mineral density; and at times prescribed for PMDD symptoms; acne and hirsutism; heavy menstrual bleeding. (Cheslak-Postava, 2014)

Do Hormonal Contraceptives Increase Risk of Depression?

- One million women in the Denmark national registry, followed for 6.4 years (Skovlund, 2016), ages 15 to 19 years old had a higher risk of depression, even when they had no history of depression.
 - The hormonal contraceptive group age 15-19 had an increased relative risk of 1.7 of the first incidence of depression diagnosed in a psychiatric hospital
 - The hormonal contraceptive group age 15-19 had an increased relative risk of 1.8 of the first incidence of using an antidepressant
 - Hard numbers are for the non-use, 10k prescriptions of antidepressants over 1.1 million person years vs use of oral combined 18.5k antidepressant prescriptions over 0.91 million person years (RR 1.8).

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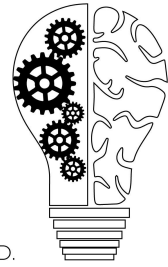
- The all progestin-only pill group age 15-19 had a 2.2 risk of first time antidepressant and 1.9 first diagnosis of depression in a psychiatric hospital
- Risk did not increase till 2 months after initiation of hormonal contraceptive use, peaked at 6 months and after one year decreased significantly
- Another study of 1236 women, ages 20-39 from the United States National Health and Nutrition Examination Survey (NHANES) found that “women who had used OC during adolescence showed an at least 1.7 times higher 1-year prevalence of depression in adulthood compared to both women who had never used OC, and to women who had only started using OC after adolescence.” (Anderl, 2017)

Some critics:

- Large-cohort population, based studies (especially if the data is from an administrative database) have more chances to find a statistically significant result even if the results are not clinically significant. However in the Denmark study, all correlations showed similar things which would not occur if there was no link, and relative risks were high, especially for adolescent women.
- Are women who are accessing hormonal contraceptive methods accessing more health care systems in general?
- Previous studies looking at rates of depression did not find a correlation with OCPs or some even reported improvements in mood. Months earlier there was a systematic review study published in the European Journal of Contraception and Reproductive Health Care. Although they made it clear that we were lacking prospective studies, the data that did exist at the time showed no correlation between hormonal contraception and women’s moods, or actually had improvement in mood. Therefore, this new study has to be weighed along with the rest and can not replace all prior research.
- In the study, it states that for every 100 women who did not use hormonal birth control, 1.7 were later prescribed an antidepressant. For every 100 who did use, 2.2 were prescribed antidepressants. The difference is 0.5 percentage points meaning that if this was a randomized control trial, for every 200 women treated,

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one needed to be treated with an antidepressant.

(Carrol, 2017- New York Times)

- The amount and types of progesterone hormone varies between different hormonal contraceptives. (Antiandrogenic progesterones are less possible to cause mood lability, lower chances of acne, and lower chances of increased appetite or weight gain.)
- We should not underestimate the role of molecular genetics in determining effects of hormonal contraceptives on women.
- “This study showed an association between birth control and depression. Specifically, both women who took oral contraceptives (which go through the bloodstream and to the whole body) and women who had progesterone IUDs (such as the Skyla or Mirena, which concentrate hormones in the uterus) seemed to have higher rates of depression. But like all epidemiologic studies, it can only prove that there is some correlation between hormones and depression (and only in this particular data set), not that one causes the other.” David Grimes, MD

Pathophysiology: How do OCPs work in general compared to natural states of hormonal secretions?

1. Hormonal levels

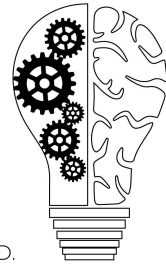
- We want to weigh the effects of amounts of hormones vs effects of pulsatility of hormones.
- OCPs have much smaller levels of estrogen and progesterone (progesterone > estrogen) compared to a natural woman’s cycle.
- In general, progesterone is more causative for depressive episodes and estrogen is more causative in elevations in mood. Antiandrogenic progesterones are said to be causing less of mood lability and negative emotional effects.

2. Mode of secretion

- In the past it has been stated rapid declines in hormones have a negative impact on mood.

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- In natural circumstances, the arcuate nucleus of the hypothalamus functions as a pulse generator, resulting in the hourly release of gonadotropin releasing hormone (GnRH) into the hypothalamic-pituitary portal vasculature.
 - This leads to a pulsatile plasma profile of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
 - LH and FSH lead to a pulsatile increase in estrogen and progesterone.
 - The pulsatile fashion of LH and FSH also regulates the growth and maturation of the graafian follicle in the ovary.
 - Our neural clocks termed the hypothalamic GnRH pulse generator determines the pulse frequency but the amount of GnRH released in each pulse is determined by our estrogen and progestins.
- OCPs steady state inhibits GnRH, therefore, there is a lower level of estrogen and progesterone and no longer rapid shifts in estrogen and progesterone.
- In one study, triphasic OCPs (which correlate more to natural menstrual cycles) were more related to first episode depression than monophasic ones. (Cheslak-Postava, 2014)

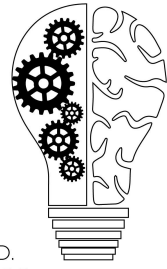
3. Feedback mechanisms

- In a natural menstrual cycle, we have both negative AND positive feedback mechanisms involved. Approaching mid-cycle, we have a 36 hours increase in levels of estrogen which leads to a surge in FSH, LH further to which we have a second surge in estrogen this time accompanied by progesterone prolonging through the second half of the cycle.
- OCPs solely act by negative feedback, decreasing hormonal states on all 3 levels therefore resulting in a much decreased states of estrogen and progesterone hormones. The low steady fashion of hormone exposure with OCPs, prevents FSH and LH surges and therefore subsequent ovulation.
- The pulsatile nature of hormonal secretions is essential for positive feedback mechanisms leading to maintenance of normal ovulatory menstrual cycles.
- Women are most euphoric around their ovulatory phases.

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- OCPs prevent ovulation by providing a steady level of hormonal exposure, therefore, preventing the body to go through the plasma surges of the FSH/LH and subsequently the sex steroids. Because of this effect, women on OCP are deprived of the natural mood elevations experienced around and post time of ovulation.

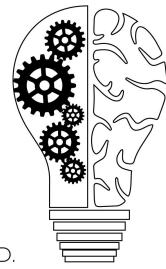


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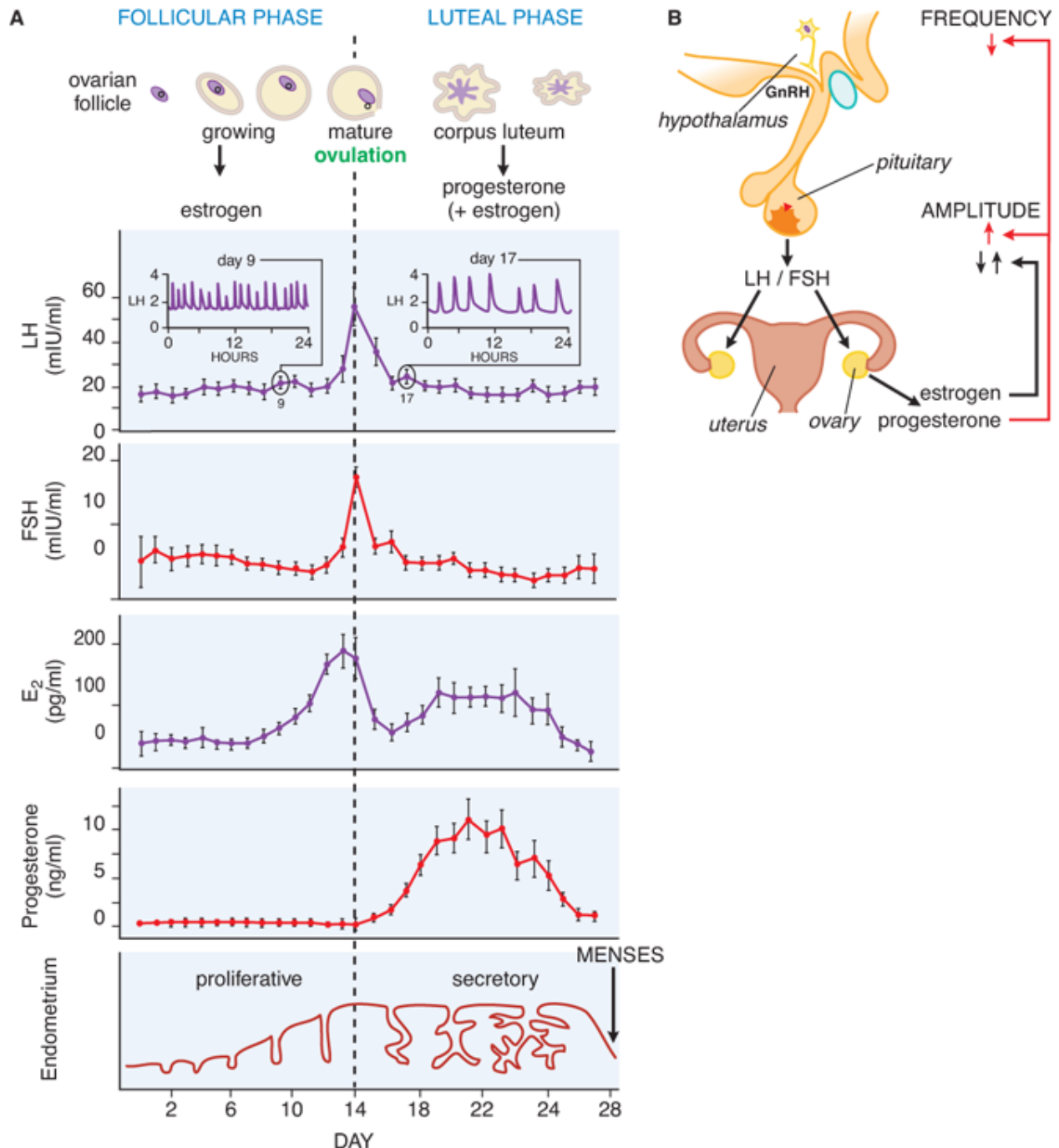
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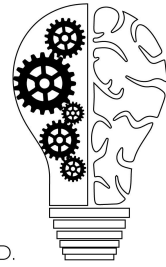
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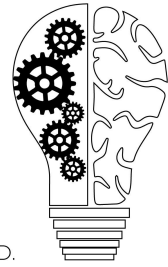
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Point 2: OCP Have Unique Effects on the Brain

- Hormonal contraceptives cross the blood brain barrier
- Pulsatile nature of natural hormones
- In puberty, the surges of sex hormones cause organizational changes in the brain (Peper, 2011)
 - “Typical gray matter decreases in prefrontal, parietal, and temporal cortices taking place during puberty and adolescence were found to be related to increased levels of estradiol in girls and to increased levels of testosterone in boys.”
- OCP bind receptors in different brain regions
 - Immediate changes (seconds to minutes)
 - Decreased endogenous estrogen and progesterone
 - Estrogen inhibits secretion of FSH
 - Progesterone inhibits secretion of LH
 - Absence of normal fluctuations
 - Strongly reduced testosterone levels (to the level of follicular phase)
 - Decreased effect of oxytocin on social-reward processing
 - Epigenetic processes (takes months)
 - 28 women, ages 16 to 35, on hormonal contraception for 3 months were compared to controls and found to have these differences in the brain on MRI. (Lisofsky, 2016) The women on contraceptives had decreased gray matter volume in the left amygdala/anterior parahippocampal gyrus.
 - Sex steroid hormones have effects on the cortical and subcortical regions involved in cognitive and emotional processing. The addition of progesterone to hormone therapy has been shown to cause adverse mood effects in women. Mechanisms include: activation of (Y aminobutyric acid A) GABA-A receptor which is the major inhibitory system in the central nervous system (CNS) of humans. Also, external progestins more than natural progesterone, increase levels of monoamine oxidase which degrades serotonin concentrations. (Kleiber, 1996)

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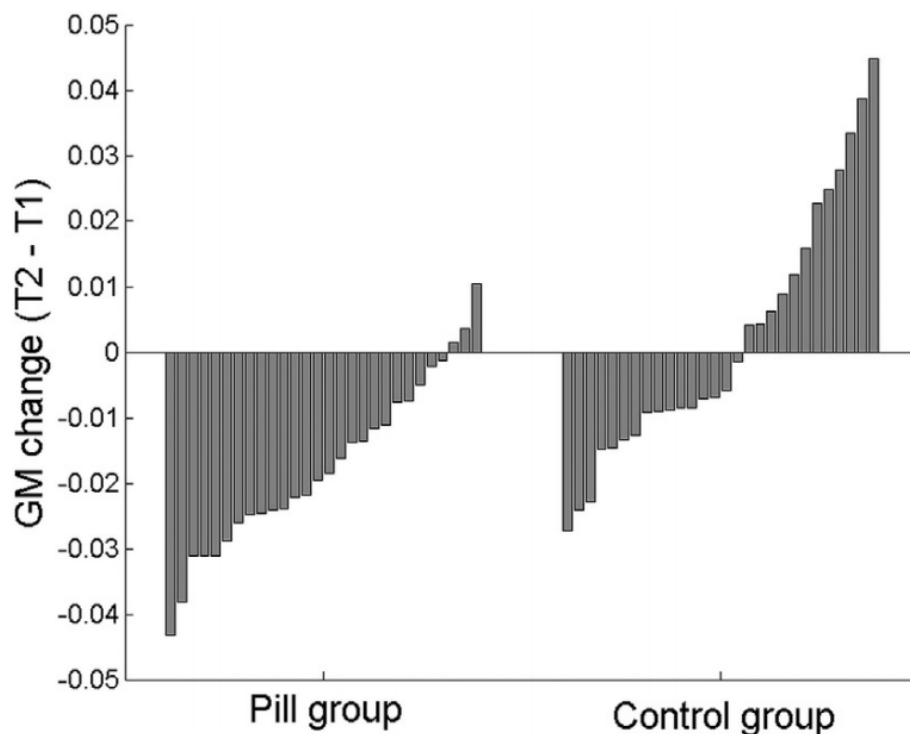
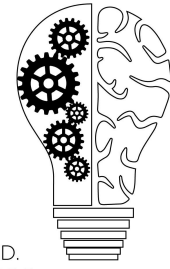


Fig. 5. Individual change scores for gray matter (GM) volume in the amygdala/anterior parahippocampal gyrus.

- Hormonal contraceptives decrease the ability to have fear extinction
 - Women have 2x the rate of anxiety disorders, compared to men, specifically starting after puberty
 - Estrogen can reduce fear, by enhancing fear extinction
 - A single dose of estrogen can reduce fear extinction
 - Low estrogen levels are associated with higher fear conditioning
 - In one study, women with lower estrogen when showed a violent video, on subsequent days had elevated skin

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conductance and when going through a fear extinction task and also had stronger intrusive memories (Wegerer, 2014)

- High estrogen facilitates fear extinction and protects against the effects of stress by causing:
 - increased activation of the ventromedial prefrontal cortex (vmPFC)- amygdala circuit during fear extinction
 - Increased activation of anterior cingulate cortex (ACC) and dorsolateral PFC during emotional response inhibition important in fear regulation
 - Downregulation of emotional and stress reactivity in the amygdala, hippocampus, hypothalamus, ACC, orbitofrontal cortex
- Women on OC during fear extinction:
 - Displayed higher activation in the amygdala, thalamus, ACC, and vmPFC, and also had slower habituating skin conductance responses, which could suggest impaired fear extinction
- Women on OC had decreased reactivity of HPA axis (hypothalamic-pituitary-adrenal axis):
 - When cortisol was given to women on OCs, they had increased hippocampal activation during a fear condition whereas in men or naturally cycling women had decreased activation.
 - When in a non-stressful situation OC users had decreased amygdala activity towards negative pictures (Petersen, 2015)

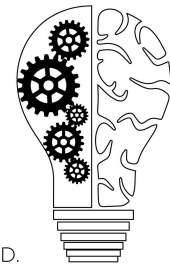
Empathy

- A single dose of estrogen in one study increased men's empathy (increased physiological response to another's pain, increased emotional (vicarious) reactivity) (Olsson, 2016)
- A recent systematic review concluded that facial emotional processing is enhanced during the follicular phase and oral contraceptives decreased brain

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responsiveness during different facial emotion processing tasks. Postpartum and pregnant women may be in a hypervigilant state in regards to facial emotion processing. (Osorio, 2018)



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Reward Pathways

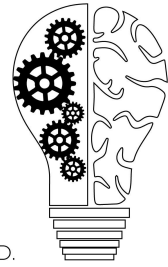
- Estrogen increases reward pathways by increasing dopamine whereas OC dampen reward processing changing social and sexual stimuli

Partner Selection and Relationship:

- Women during ovulation had a preference for more masculine faces, those on OCs did not have a change in preference during the cycle. (Penton-Voak, 1999)
- Women have a preference of more masculine bodies when their fertility is highest (Little, 2007)
 - Other preferences include: vocal masculinity, video clips of dominant behavior, taller men
 - Change in behavior seen: greater interest in public events where they could meet men, more sexual fantasies
- Women during ovulation are more attracted to more masculine male faces. This was a study of 42 female volunteers at 2 different phases of their menstrual cycle. In general, women favored a more masculine face but during ovulation there was an increased choice for the more masculine face. (Johnston, 2001)
- In women during the period before ovulation, testosterone normally predicts preference for masculine faces, but in women on OCs there was no link (Bobst, 2014)
- Preferences change in marriage when women get off of their OCs, if their partner is unattractive they may remain with higher dissatisfaction and if their partner is attractive they will have higher satisfaction (Russell, 2014)
- Another study found that highest sexual satisfaction in women was found in those who either met their partner when not on OC and did not get on an OC or those who met their partner on an OC and continued on an OC (Roberts, 2014)

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Citations and Further reading:

Further reading on IUD: [article](#) showing how uncommonly IUDs are used in the US

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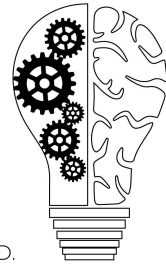
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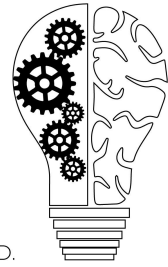
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Appendix:

- OCPs have more progesterone than estrogen. They only have small amounts of estrogen to stabilize endometrial lining and to reduce bleeding.
- OCPs in general cause improved quality of life by different means for example by reducing bleeding.
- Due to the molecular genetic phenomena, if one OCP not satisfactory, changing to a different one might be a solution.
- IUDs are not systemically absorbed; therefore, do not inhibit ovulation. They mainly act by inflammatory responses in uterus preventing implantation of the ovum. They also act by increasing cervical mucosal thickness.
- Copper IUDs act by the same inflammatory responses, also copper elements in the device are said to have paralyzing effects on sperms.